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Using Data to Guide Policy: Next Steps for Preventing Perinatal Hepatitis B Virus Transmission in Cambodia

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1. Introduction

Hepatitis B virus (HBV) infection is highly endemic in Cambodia with chronic HBV infection prevalence among adults ranging from 8% – 13% [1]. In highly HBV endemic countries, perinatal and early childhood are predominate periods for acquiring chronic HBV infection. A mathematical model to estimate hepatitis B disease burden has been developed using HBV infection markers related to perinatal and early childhood infection risk [2]. Model assumptions for Cambodia and other countries with similar HBV epidemiology included 11.8% hepatitis B surface antigen (HBsAg) prevalence among women of childbearing age, 30% hepatitis B e-antigen prevalence among HBsAg-infected women, and 25% hepatitis B core antibody prevalence among 5 years olds. With these assumptions it is estimated that 40,000 chronic HBV infections and 5,000 HBV-related deaths would occur per birth cohort in Cambodia in the absence of vaccination

Chronic hepatitis B infection can be prevented with vaccination. Clinical trials show >95% of infants and children show a protective immune response after three doses of hepatitis B vaccine [3]. Furthermore, randomized controlled trials of vaccination at birth found that infants born to mothers with chronic hepatitis B infection were 3.5 times less likely to become infected with HBV [4]. These data showing that hepatitis B vaccine is effective for post-exposure prophylaxis are the basis for the WHO recommendation to administer the first dose of vaccine as soon as possible, preferably within 24 hours of birth [5].

To address their hepatitis B disease burden, Cambodia has adopted both routine infant vaccination and birth dose vaccination strategies for preventing perinatal and childhood

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HBV infection. A 3-dose hepatitis B vaccination schedule (6, 10 and 14 weeks) was adopted in 2001 and vaccination of newborns within 24 hours was adopted in 2006. In 2010, Cambodia reached 85% 3-dose hepatitis B vaccine coverage [6]. The rapid progress in increasing coverage was related to the minimal training or other programmatic adjustments needed since a combination vaccine of containing diphtheria, tetanus, pertussis (DPT) antigens was replaced with one that contained DPT and hepatitis B antigens.

Although steadily improving, timely birth dose coverage was only 68% in 2011 [7]. Introducing a timely birth dose requires setting new standards and coordination between the immunization programme and health care sectors that generally do not routinely administer and manage vaccines. High timely birth dose coverage is also more difficult to achieve among births occurring outside of health facilities. In 2010 in Cambodia, 54% of newborns were born in health facilities, an increase from 21% in 2005 [6, 8]. This increase is largely a result of a Ministry of Health initiative started in 2007 to encourage facility deliveries by providing a midwives a financial incentive to deliver newborns in facilities [9]. In addition, midwives are known to share their incentive with traditional birth attendants upon referral to them for facility delivery. These on-going efforts to increase facility births will lead to reduction in maternal and neonatal mortality and will also benefit perinatal hepatitis B prevention if the practice of timely hepatitis B birth dose vaccination at all facilities is fully adopted.

No systematic assessment has been conducted in Cambodia that examines the delivery of hepatitis B vaccine at birth in healthcare facilities. This paper reports on an assessment that aimed to estimate timely birth dose coverage among facility births and provide guidance to strengthen the prevention of newborn HBV infection through timely administration of a hepatitis B vaccine birth dose.

2. Methods

This assessment was designed to survey multiple provinces to capture the range in practices that may be adopted throughout the country and across facility types. A total of ten of Cambodia's 24 provinces were selected and the final number of facilities selected in the survey was determined by selecting 1–3 facilities of each type in each province. Specifically in each province, one provincial hospital (and its referral health centre), 1–2 district hospitals (and its referral health centre), two to three additional health centres, and where possible 1–2 private maternity clinics were enrolled. District hospitals were selected based on (1) being in a district other than the one with the province hospital and (2) having the highest number of deliveries. The two additional health centres per province were selected based on having the highest and lowest number of deliveries. Private facilities were selected from among those that receive free hepatitis B vaccine from the national immunization programme.

Ministry of Health staff were trained to use a structured questionnaire for data collection. Numbers of births were collected from birth registries. Infant vaccination data was collected from vaccination log books, immunization and maternity staff were interviewed about hepatitis B vaccination policy, practices and knowledge, and observations of vaccine

handling and storage were recorded; if a facility referred vaccination off-site, these data were collected from the referral site.

Two estimates of hepatitis B birth dose coverage were calculated: 1) coverage of vaccine administered within 24 hours of birth (timely birth dose), 2) coverage of vaccine administered within 7 days of birth (<7 day coverage). Coverage was calculated for each facility using capture-recapture methodology. This involved selecting 25 random children from the facility birth registry starting with the most recent birth and selecting every 10th child until 25 names were recorded (capture). The vaccination status of the 25 newborns selected were then sought from vaccination logs either on-site or at the referral site where hepatitis B vaccinations are given (recapture). Survey teams were instructed to avoid collecting data from periods where there may be vaccine shortage to better estimate coverage assuming adequate vaccine supply. Although data collection occurred in September 2011, data collected could reflect vaccines administered as much as three months prior.

If a selected facility referred vaccination off-site, data were analysed as being from the original selected facility even though immunization data were collected from the referral facility. Therefore, referral sites visited are not included as separate sites and are not counted in the sample size. Findings from the provincial and district hospitals were similar and were therefore combined for the presentation of results.

Data were entered into an Epi-Info v.3.5.1 (Atlanta, GA, USA) database and analysed using SAS v9.2 (Cary, NC, USA). Frequencies and percentages, medians and interquartile ranges (IQR) of vaccine coverage by category were calculated. To assess associations between categorical variables 2-tailed Fisher's exact p-values were calculated. To assess differences in continuous variables Wilcoxon rank-sum p-values were calculated to compare two groups and Kruskal Wallis p-values were calculated for more than two groups.

This was a Ministry of Health-funded project with in-kind technical assistance by World Health Organization and US Centers for Disease Control and Prevention. This assessment was for program evaluation and was exempt from institutional review board review.

3. Results

Fifty-one health facilities were visited in ten provinces. Fifty facilities had records on numbers of births in the three full months prior to the assessment; together these facilities deliver an estimated 37,000 newborns annually. Two hospitals did not have interviews conducted at the referral health centre and therefore are missing vaccination knowledge and practice data; one health centre did not have accessible log books and is therefore missing vaccination coverage data.

Ten (20%) of the facilities were provincial hospitals, 11 (22%) were district hospitals, 24 (47%) were health centres, and 6 (12%) were private facilities. A total of 66 interviews were conducted among facility health care providers including 12 (18%) physicians, 26 (39%) nurses, 24 (36%) midwives, 3 (5%) medical assistants, and 1 (2%) pharmacist.

3.1. Vaccination Coverage

Based on capture-recapture data from 50 facilities and 1250 births, median (IQR) timely hepatitis B birth dose coverage was 66% (48%–92%) and median <7 day coverage was 82% (56%–96%) (Table 1). Both timely birth dose coverage and <7 day coverage were lower in hospitals than in private facilities (24 hours $p=0.02$; 7 day $p=0.02$) and health centers (24 hours $p=0.002$; 7 day $p=0.0003$) (Table 1).

A total of 34 (66%) facilities provide hepatitis B birth dose vaccination on-site and 17 (34%) facilities referred vaccination off-site. Seven (70%) provincial hospitals and 10 (91%) district hospitals did not vaccinate on-site. Facilities with on-site vaccination had a median (IQR) timely birth dose coverage of 88% (60%–90%) compared with 48% (20%–52%) among facilities referring vaccination off-site (Wilcoxon rank-sum p -value <0.0001). Similar findings were observed for <7-day coverage (Table 1).

Median (IQR) timely birth dose coverage was 96% (90% – 100%) at the 12 (35%) facilities administering hepatitis B vaccine on-site and on the delivery ward compared with 72% (56%–92%) among facilities administering hepatitis B vaccine on-site but in a separate part of the facility, such as outpatient department or routine immunization room (Wilcoxon rank-sum p -value <0.0001). Similar findings were observed for <7-day coverage. (Table 1)

3.2. Factors related to giving birth dose on-site

The birth dose was administered on-site at 4 (19%) of hospitals compared to 24 (100%) of health centres and 6 (100%) of private facilities. Of the 12 facilities where vaccination was provided specifically on the delivery ward, 2 (10%) were hospitals, 6 (25%) were health centres, and 4 (67%) were private facilities.

The 12 facilities providing the birth dose on the delivery ward were asked for reasons why; 7 (58%) reported the national birth dose policy, 7 (58%) reported demand for the vaccine among patients, and 6 (50%) reported vaccinating on the delivery ward is a best practice.

The 17 facilities not providing the birth dose on-site were asked for reasons why not; 11 (65%) reported they had no instruction to do so, 2 (12%) reported it was not their responsibility, and 1 (6%) reported not having staff to implement. These facilities were also asked what would be needed to implement vaccination on-site; 15 (88%) reported they would need training, 11 (65%) reported they would need a refrigerator, and 2 (12%) reported they would need more staff.

3.3. Factors related to late or missed vaccination

Factors that could contribute to late or missed vaccination commonly reported at health facilities including misunderstanding of contraindications, charges for vaccination, vaccination services not available at all times, shortages of vaccine stock, mothers refusing vaccine, low knowledge or training among staff (Table 2). Of 21 (43%) facilities reporting shortages of vaccine stock, 20 reported one shortage in the past three months, and one reported more than one shortage. Of 16 (33%) facilities that reported not having vaccination services available at all times; 12 (24%) did not vaccinate in evenings and 14 (28%) did not vaccinate on weekends. Factors related to late or missed vaccination were similar in

hospitals, health centers and private facilities, except health centres were more likely than other facilities to charge a vaccination fee to mothers delivering in facility ($p < 0.0003$), hospitals were less likely than other facilities to have vaccination services available at all times ($p=0.02$), vaccine stock shortages were more common in hospitals or their referral sites and hospitals were more likely than other facilities to have low knowledge or training among staff ($p=0.07$) (Table 2).

Among the 17 facilities (all hospitals) that referred vaccination off-site, 12 (71%) reported that at least 75% of women stayed at least one day in the hospital, Overall, 16 (94%) hospitals that referred vaccination off site advised mothers to have newborns vaccinated with hepatitis B vaccine and where to get vaccinated; however, 5 (29%) did not tell mothers vaccination should take place within 24 hours of birth, and 6 (35%) discharged mothers when no vaccination services were available for infants to receive the birth dose.

4. Discussion

Cambodia has made remarkable advances in increasing hepatitis B vaccination coverage during the past decade. However, this assessment showed that median timely birth dose coverage among newborns born in facilities was only 66%. Assuming birth dose is followed by two additional timely doses, 9% chronic HBV infection prevalence among women of childbearing age, and 54% of births occur in facilities [6], an estimated 3,000 perinatal infections would be prevented each year in Cambodia if timely birth dose coverage was increased in health facilities from 66% to 100% [2].

There are two main systems for administering the hepatitis B vaccine birth dose to newborns born in facilities in Cambodia. Either the birth dose is given on-site within the facility that the infant is born at, or it is given off-site in a nearby health facility that is separate from where the birth took place. This assessment found that timely birth dose coverage was significantly higher in facilities that administer birth dose vaccine on-site (88%) compared with facilities that referred infants for off-site vaccination (48%). This finding is consistent with the identification of barriers to timely birth dose coverage among facilities referring vaccination off-site; these include that the mother might stay in the delivery facility >24 hours which would preclude the chance of timely vaccination off-site, off-site vaccination services may not be available at time of discharge (i.e., weekends or evenings), and delivery facilities might not always remind mothers to have her newborn vaccinated within 24 hours. Some hospitals that refer vaccination off-site adopted the innovative practice of having a family member take the newborn to the referral vaccination site if mother is not discharged within 24 hours. However, this effort did not yield birth dose coverage as high as coverage in hospitals vaccinating on-site, and might promote early separation of mother and newborn and disrupt initiation of breast feeding.

In Cambodia, vaccination is generally not a responsibility covered by hospital staff. Hospitals were more likely to refer vaccination off-site compared with health centres and private facilities. This assessment found the main reason for not providing on-site vaccination was lack of policy or guidance to provide the birth dose in hospitals. Therefore, these data support the need to strengthen national guidelines for hospital staff to administer

the hepatitis B vaccine birth dose to newborns. However, establishing policies for vaccination in delivery facilities alone may not be sufficient for complete implementation. Studies from China describe the uneven adoption of vaccination policies at delivery facilities. When midwifery and obstetric staff were given the responsibility to administer hepatitis B birth dose vaccination to newborns delivered in health facilities, surveys in central and eastern provinces found 73% and 82% birth dose coverage respectively, while western provinces had only 50% coverage [10]. An assessment conducted in rural areas of four western provinces reported that a major reason for low coverage was poor coordination between immunization and hospital midwifery staff [11]. A similar conclusion was made from an assessment in Vietnam [12].

Other assessments have shown that having a written hospital policy or standing orders for newborn hepatitis B vaccination is associated with having higher vaccination coverage in facilities [13, 14]. Therefore, in addition to strengthening national guidance, hospitals should have policies in place to provide on-site birth dose vaccination. Regarding specifics on the responsibility of vaccination, this assessment found higher coverage among facilities vaccinating in the delivery ward compared with vaccinating elsewhere on-site. Vaccinating in the delivery ward facilitates clear designation of a person responsible for vaccination who will be consistently available and who can integrate vaccination as part of the early essential newborn care activities. On the other end of the spectrum, vaccination at or near discharge can lead to missed vaccinations when the responsible person is not available and mother and baby are otherwise clear for discharge [15].

This assessment revealed that training is needed to ensure correct understanding of contraindications and improve knowledge of mother-to-child transmission of the hepatitis B virus. Health care facilities of all types reported not vaccinating premature neonates, low birth weight neonates, and neonates born to HIV- positive mothers. None of these contraindications exist in Cambodia immunization policies nor in WHO recommendations on hepatitis B vaccination [5]. Administration of birth dose vaccine as part of essential newborn care should also be included in the educational curricula of midwives and obstetrics.

This evaluation has a few important limitations. Facility selection was based on convenience and the assessment was performed in only 10 of 24 provinces; therefore, findings may not be generalizable to other healthcare facilities and provinces. Only one or two health care workers were interviewed at each facility and they may not reflect the knowledge and practices of all health care workers in the facility. Survey teams may not have been able to completely skip over vaccine shortage periods when collecting data for estimating vaccine coverage. The data calculated represent an underestimate of vaccination coverage as it assumes that children that were not in the vaccination log book were not vaccinated when they could have been vaccinated at another facility.

This assessment provides clear data to support actions for increasing birth dose coverage in facilities, especially for supporting development of national guidance and facility-based policies for administering timely birth dose on-site and preferably on delivery wards. Strengthening policies and practices for vaccinating all newborns born in facilities will go a

long way in Cambodia given the successful and ongoing efforts for increasing facility births [6, 8, 9]. It is promising that almost all facilities reported they would not need more staff to provide birth dose vaccination on-site. And finally, training including improving knowledge on the appropriate contraindications to vaccination and provision of timely birth dose as part of essential newborn care will be important next steps towards strengthening protection against perinatal HBV infection in Cambodia.

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TABLE 1

Median (interquartile range) of hepatitis B birth dose vaccination coverage among newborns based on capture-recapture methods among 50 health facilities in 10 provinces in Cambodia, 2011

Site Characteristic	Sample Size	% Vaccinated: Median (Interquartile Range)	
		<24 hour birth dose coverage	<7 day birth dose coverage
Overall	50	66 (48–92)	82 (56–96)
Type of facility			
Province or District Hospital	21	52 (24–56) ^c	60 (36–72) ^c
Health Centre	23	84 (60–92)	88 (80–96)
Private facility	6	78 (76–100)	100 (96–100)
Vaccination Policy			
On-site	33	88 (60–96) ^b	92 (80–100) ^b
Refer Off-site	17	48 (20–52)	52 (28–64)
On-site vaccination policy			
Delivery ward	12	96 (90–100) ^b	100 (90–100) ^b
Elsewhere on-site	21	72 (56–92)	88 (80–92)

^a One facility could not access log books for collecting capture-recapture data

^b Wilcoxon rank-sum test p-value < 0.02 comparing the medians across subcategories of site characteristics

^c Kruskal Wallis p-value < 0.03 comparing the medians across subcategories of site characteristics

TABLE 2

Factors that could contribute to late or missed hepatitis B birth dose vaccination among health facilities in ten provinces in Cambodia, 2011

Factor	Total Sample Size	Number (%)				Fisher Exact p-values ^b
		Overall	Hospitals	Health Centres	Private Facilities	
Misunderstanding of contraindications						
Do not vaccinate low birth weight babies	48	18 (38%)	8 (44%)	8 (33%)	2 (33%)	0.77
Do not vaccinate premature babies	49	13 (27%)	6 (32%)	6 (25%)	1 (17%)	0.82
Do not vaccinate babies born to HIV-positive mothers	48	6 (12%)	2 (11%)	3 (13%)	1 (17%)	0.77
Charge for vaccination if born in facility	44	8 (16%)	4(21%)	0 (0%)	4 (67%)	0.0003
Charge for vaccination if born outside of facility	44	6 (14%)	4(22%)	2 (8%)	0 (0%)	0.54
Vaccination services not available at all times	49	16 (33%)	10(56%)	6 (25%)	0 (0%)	0.02
Facilities have had vaccine stock in last 3 months	49	21 (43%)	11(58%)	8 (33%)	2 (33%)	0.24
Facility reports mothers sometimes refuse vaccine	49	5 (10%)	3 (16%)	2 (8%)	0 (0%)	0.67
Low knowledge or training among facility staff						
No training on birth dose vaccination	49	12 (24%)	8 (42%)	3 (13%)	1 (17%)	0.07
Staff did not know mother can pass virus to baby	48	8 (17%)	4 (22%)	2 (8%)	2 (33%)	0.18

^aTwo facilities were missing data on factors contributing to late or missed vaccinations;

^bComparing proportions across facility type Bold font refers to significant findings